REMARKS

Upon entry of the amendments submitted herewith, claim 1 will be pending in this application. Claim 1 is under examination. Claims 2-9 have been canceled without prejudice or disclaimer to the subject matter claimed within.

Applicants, by canceling or amending any claims herein, make no admission as to the validity of any rejection made by the Examiner against any of these claims. Applicants reserve the right to reassert any of the claims canceled herein or the original claim scope of any claim amended herein, in a continuing application.

Claim 1 has been amended to recite "An autoclaved sterile aqueous suspension comprising ciclesonide and hydroxypropylmethylcellulose, wherein the concentration of the ciclesonide after it is autoclaved is 95% or more compared to that before it is autoclaved."

This amendment has basis in the specification on page 9 in "Example 1", as well as on pages 9-11 in "Investigation 1", "Table 1" and "Investigation 2". Further, the alleged "trademark/tradename" "hydroxypropylmethylcellulose 2910" has been deleted in favor of the chemical name "hydroxypropylmethylcellulose" solely to overcome the rejection under 35 U.S.C. §112, 2nd paragraph.

No new matter has been added within the meaning of 35 USC § 132.

In view of the following, further and favorable consideration is respectfully requested.

I. At page 4 of the Official Action, claim 1 has been rejected under 35 USC § 103(a) as being anticipated by Karlsson et al. (US Patent Publication No. 2002/0065256) in view of the MSDS for Metolose 60SH.

The Examiner asserts that the Karlsson et al. reference describes each and every

element of pending claim 1. In view of the aforementioned claim amendments and remarks set forth herein, this rejection is respectfully traversed.

a. No prima face case of obviousness

To establish a *prima facie* case of obviousness, the PTO must satisfy three requirements. First, there must be some motivation or teaching in the references cited by the Examiner to combine the separate elements taught in the separate references. As the U.S. Supreme Court held in *KSR International Co. v. Teleflex Inc. et al.*, 550 U.S. 398 (2007), "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions. ...it [may] be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. ...it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does... because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." *See KSR International Co. v. Teleflex Inc. et al.*, 550 U.S. 398 at 417-418. Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991). Lastly, the prior art references must

teach or suggest all the limitations of the claims. *In re Wilson*, 165 USPQ 494, 496 (C.C.P.A. 1970).

Currently amended claim 1 is directed to "An autoclaved sterile aqueous suspension comprising ciclesonide and hydroxypropylmethylcellulose, wherein the concentration of the ciclesonide after it is autoclaved is 95% or more compared to that before it is autoclaved."

Karlsson et al. do not teach each and every element of the currently amended claims as required by *In re Wilson*.

First, applicants respectfully note that the currently amended claims recite "An autoclaved sterile aqueous suspension...". Karlsson et al. do not teach such an autoclaved sterile aqueous suspension product. In fact, Karlsson et al. do not teach autoclaved products at all. Rather, Karlsson et al. teach the "effective sterilization of dry glucocorticosteroids can be carried out at a significantly lower temperature than that considered necessary for the heat sterilization of other substances." *See* Karlsson et al. [0012]

Further, Karlsson et al. only teach that glucocorticosteroids can be heat treated as a dry powder. Only after the glucocorticosteroid is sterilized is it added to a pharmaceutical formulation such as a suspension. In this regard, Karlsson et al. teach "there is provided a process for the sterilization of a glucocorticosteroid, which process comprises heat treating the glucocorticosteroid in the form of a powder at a temperature of from 100 to 130° C... preferably for up to about 24 hours, more preferably up to 10 hours, e.g. from 1 to 10 hours." *See* Karlsson et al. [0013] (emphasis added)

Further, Karlsson et al. teach in [0044] that "[a] sterile pharmaceutical formulation comprising a glucocorticosteroid...sterilized according to the present process, can be

prepared by mixing the sterilized glucocorticosteroid with any suitable ingredient, e.g. a surfactant, a pH regulating or chelating agent, an agent rendering the suspension isotonic or a thickening agent. All components, other than the glucocorticosteroid, can be produced by sterile filtration of their aqueous solutions." (emphasis added)

Applicants also note the Examples contained in the Karlsson et al. reference. Example 1 in paragraph [0048] states that "[n]ine 50g batches of micronized budesonide...were subjected to the heat treatment shown in Table 1 in a dry sterilizer...". Example 2 in paragraph [0051] states that the samples used therein "was subjected to a temperature of 110°C for 3 hours and 10 min ... using the same technique as in Example 1."

In Example 4, Karlsson et al. introduced the already sterilized, dry glucocorticosteroid into a formulation. In paragraph [0056], Karlsson et al. state that "[a] formulation comprising finely divided budesonide sterilized by the method of Example 2...was prepared by mixing the following ingredients..." Particularly relevant is the disclosure of Karlsson et al. in paragraph [0057] which states: "[a]ll the components, other than the budesonide, were produced by sterile filtration of their aqueous solutions and an appropriate volume of the resulting suspension (about 2ml) was filled under aseptic conditions into presterilized 5ml containers to produce a sterile product." (emphasis added)

Therefore, it is absolutely clear that the Karlsson et al. reference teaches a completely different product than what is presently claimed. Again, the presently pending product claims are directed to "An autoclaved sterile aqueous suspension comprising ciclesonide and hydroxypropylmethylcellulose, wherein the concentration of the ciclesonide after it is autoclaved is 95% or more compared to that before it is autoclaved."

In summary, Karlsson et al. do not teach an autoclaved sterile aqueous suspension product. Instead, Karlsson et al. teach the pre-treatment of a dry glucocorticosteroid and then mixing it with other elements that have been subjected to sterile filtration.

Nowhere does Karlsson et al. teach the presently claimed product – "An autoclaved sterile aqueous suspension comprising ciclesonide and hydroxypropylmethylcellulose, wherein the concentration of the ciclesonide after it is autoclaved is 95% or more compared to that before it is autoclaved."

Accordingly, Karlsson et al. does not teach each and every element of the presently claimed invention as required by *In re Wilson*. Further, Karlsson et al. provides absolutely no teaching that would motivate the skilled artisan to prepare the presently claimed product as required by *KSR*. Without such teaching, there can be no such expectation of success as required by *Amgen v. Chugai*.

These deficiencies are not remedied by the secondary reference – the Material Safety Data Sheet (MSDS) for Metalose 60SH.

Specifically, the MSDS discloses various properties of hydroxypropylmethylcellulose Metalose 60SH. It does not contain any disclosure regarding an autoclaved sterile aqueous suspension comprising ciclesonide as presently claimed.

Therefore, no *prima facie* case of obviousness has been established over the presently pending claims.

b. Unexpected results

Further, even if the Examiner would have established a *prima facie* case of obviousness, it is rebutted by the data presented in Table 3 on page 14 of the present

specification. The data illustrates that the improvement achieved by the presently claimed subject matter is more than the routine optimization of parameters that a person of ordinary skill in the art would have employed.

It is known in the art that drug content uniformity, *i.e.* uniform drug concentrations sampled from the upper, middle and lower portion of the suspension, of an aqueous suspension containing a water-insoluble drug tends to be decreased by autoclaving, even if the drug is chemically stable. *See,* for example, page 3 of the present specification. Applicants submit that the presently claimed ciclesonide-containing aqueous suspension comprising hydroxypropylmethylcellulose achieved unexpectedly superior ciclesonide concentration uniformities as compared to suspensions comprising other wetting agents. Applicants respectfully draw the Examiner's attention to the data in Table 3 on page 14 of the present specification. The data in Table 3 shows ciclesonide concentration uniformity after autoclaving for a ciclesonide aqueous suspension containing hydroxypropylmethylcellulose, as recited in currently amended claim 1 and exemplified by Example 2, compared to ciclesonide aqueous suspensions containing other wetting agents. The recovery rate of ciclesonide after autoclaving was calculated by taking the ciclesonide concentration before the autoclaving to be 100%. Aliquots of the bulk suspension were sampled from the upper, middle and lower portions of a glass container. As can be seen from the calculated ciclesonide recovery rates for Example 2 and Comparative Examples 3-7, the ciclesonide aqueous suspension containing hydroxypropylmethylcellulose, as presently claimed, achieved unexpectedly superior ciclesonide concentration uniformity as compared to ciclesonide aqueous suspensions containing other wetting agents. In particular, the standard deviation of the ciclesonide

recovery rates for the upper, middle and lower portions of the bulk suspension of Example 2 is approximately 0.05%, compared to standard deviations of as high as 7% for the upper, middle and lower portions of the bulk suspension of the Comparative Examples. Accordingly, Applicants respectfully submit that the ciclesonide aqueous suspension containing hydroxypropylmethylcellulose, as presently claimed, achieved unexpectedly superior ciclesonide concentration uniformity as compared to ciclesonide aqueous suspensions containing other wetting agents.

In view of the remarks set forth herein, it is submitted that the unexpected results presented herein clearly rebuts any prima facie case of obviousness alleged by the Examiner. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this rejection.

II. At page 7 of the Official Action, claim 1 has been rejected under 35 USC § 112, 2nd paragraph as being indefinite.

The Examiner has rejected claim 1 under USC § 112, 2nd paragraph as being indefinite. The Examiner asserts that the term "hydroxypropylmethylcellulose 2910" is a trademark / tradename and is therefore indefinite within the meaning of 35 U.S.C. §112, 2nd paragraph. Applicants respectfully traverse. However, solely to overcome this rejection and to place this application in condition for allowance, applicants have canceled the objected to language and have replaced it with the specific chemical name of the rejected term. As such, the term "hydroxypropylmethylcellulose" is now presently recited in claim 1 solely to overcome this rejection.

Accordingly, applicants respectfully request that the Examiner reconsider and

withdraw this rejection.

III. At page 8 of the Official Action, claim 1 has been rejected under 35 USC § 103(a) as being unpatentable over Karlsson et al. (US Patent Publication No. 2002/0065256) in view of Nagano et al. (WO01/28563).

The Examiner asserts that the combined teachings of the Karlsson et al. reference and the Nagano et al. reference describe each and every element of pending claim 1. In view of the aforementioned claim amendments and remarks set forth herein, this rejection is respectfully traversed.

A brief outline of relevant authority is set forth above in Section I. Also, the Karlsson et al. reference is discussed in detail in Section I. For the sake of brevity, the discussion of the relevant authority and the Karlsson et al. reference is incorporated herein in its entirety.

The Examiner relies on Nagano et al. for its disclosure of a combination of ciclesonide and HPMC. However, Nagano et al. do not remedy the deficient teachings of Karlsson et al., discussed in Section I above.

Claim 1 is free of the prior art for the reasons discussed above (*See*, Section I) and applicant's arguments stated above are incorporated herein by reference in their entirety. Nagano et al. do not remedy the deficient teachings of Karlsson et al. because they do not teach an autoclaved sterile aqueous suspension comprising ciclesonide as presently claimed. In fact, Nagano et al. are completely silent regarding sterilized products. Therefore, they cannot possibly remedy the deficient teachings of Karlsson et al.

Accordingly, applicants respectfully submit that a *prima facie* case of obviousness has not been established. Thus, the Examiner is respectfully requested to reconsider and

withdraw this rejection.

CONCLUSION

In light of the foregoing, Applicant submits that the application is now in condition for allowance. If the Examiner believes the application is not in condition for allowance, Applicant respectfully requests that the Examiner contact the undersigned attorney if it is believed that such contact will expedite the prosecution of the application.

In the event this paper is not timely filed, Applicants petition for an appropriate extension of time. Please charge any fee deficiency or credit any overpayment to Deposit Account No. 14-0112.

Respectfully submitted,

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